



US006316652B1

(12) **United States Patent**
Steliou(10) **Patent No.:** US 6,316,652 B1
(45) **Date of Patent:** Nov. 13, 2001(54) **DRUG MITOCHONDRIAL TARGETING AGENTS**(76) Inventor: **Kosta Steliou**, Boston University
Department of Chemistry 590
Commonwealth Ave., Boston, MA (US)
02215

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/468,844**(22) Filed: **Jun. 6, 1995**(51) **Int. Cl.⁷** **C07F 1/10**; C07F 1/12;
C07F 15/00; C07F 3/00(52) **U.S. Cl.** **556/42**; 549/3; 514/184;
514/189; 514/492; 514/493; 514/494; 514/495;
514/501; 514/502; 514/505; 556/136; 556/43;
556/57; 556/58; 556/45; 556/46; 556/138;
556/140; 556/110; 556/112; 556/118; 556/121(58) **Field of Search** 549/3; 556/136,
556/42, 43, 57, 58, 45, 40, 138, 140, 110,
112, 118, 121; 514/184, 189, 492, 493,
494, 495, 499, 501, 502, 505(56) **References Cited**

U.S. PATENT DOCUMENTS

4,742,081	5/1988	Stracher et al.	514/547
4,866,040	9/1989	Stracher et al.	514/17
5,008,288	4/1991	Stracher et al.	514/535
5,318,962 *	6/1994	Khokhar et al.	514/184
5,348,950 *	9/1994	Hata et al.	549/3 X
6,054,271 *	4/2000	Tsien et al.	549/3 X

OTHER PUBLICATIONS

- R. B. Weiss et al., "New Cisplatin Analogues in Development: A Review" *Drugs* 46:360-377 (1993).
- M. Gordon et al., "Review of Platinum Anticancer Compounds" *J. Med.* 24: 209-265 (1993).
- L. S. Hollis, "New Approaches to the Design of Platinum Antitumor Agents" *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy*, 115-125 (S. B. Howell, ed. 1991).
- R. B. Fram, "Cisplatin and Platinum Analogues: Recent Advances" *Curr. Opin. Oncology* 4: 1073-1079 (1992).
- W. J. Brouillette et al., "Synthesis and Enzymatic Evaluation of Conformationally Defined Carnitine Analogs" *J. Org. Chem.* 59: 4297-4303 (1994).

S. V. Pande et al., "Carnitine-Acylcarnitine Translocase Catalyzes an Equilibrating Unidirectional Transport As Well" *J. Biol. Chem.* 255: 2994-3001 (1980).

M. S. R. Murthy et al., "Mechanismof Carnitine Acylcarnitine Translocase-catalyzed Import of Acylcarnitines into Mitochondria" *J. Biol. Chem.* 259: 9082-9089 (1984).

H.R. Brady et al., "Mitochondrial Injury An Early Event in Cisplatin Toxicity to Renal Proximal Tubules" *Am J Physiol*, vol. 258, No. 5 part 2, 1990, pp. F1181-F1187.

D.S. Choi et al, "The Acute Nephrotoxicity of Cis Diamminedichloroplatinum-II in Rats An Ultrastructural Observation" *Seoul J Med.*, vol. 25, No. 2, 1984, pp. 168-185.

A.F. Noels et al, "Novel platinum(II)-diaminobiotin complexes. Their systhesis and characterization" *Bull. Soc. Chim. Belg.*, vol. 100, No. 7, 1991, pp. 497-502.

IT 1 169 460 B (Sigma Industrie Farmacuetiche Riunite S.P.A.), May 27, 1987, p. 2, line 19; p. 3, line 15; table 4, p. 13.

J. E. Christman et al., "Study of the Selective Cytotoxic Properties of Cationic Lipophilic Mitochondrial-Specific Compounds in Gynological Malignancies" Abstract, table 1; paragraph: discussion: figure 8.

Im Huxham et al., "Intracellular localization of anticancer therapeutic compounds using electron spectroscopic imaging as a tool to investigate mecanisms of drug targeted cancer therapy" Database Cancerlit Cancer Institute, Bethesda, Md. AN NCI: 96616469; and *Br. J. Cancer*, vol. 71, Suppl. 24, p. 12, 1994.

M. M. Jones et al., "Control of the nephrotoxicity of cisplatin by clinically used sulfur-containing compounds" Abstract; Figurel; Tables 1-4.

* cited by examiner

Primary Examiner—Paul F. Shaver

(74) *Attorney, Agent, or Firm*—David Prashker

(57) **ABSTRACT**

The invention relates to novel targeting drug agents that are targeted for entry into the mitochondria. More specifically, the agents are cisplatin derivatives called mitoplatsins which are useful as anti-tumor agents. Mitoplatsins are named for their targeting to the mitochondrial DNA via the carnitine-acylcarnitine translocase system. The invention also relates to methods of synthesizing mitoplatsins, compositions of matter containing mitoplatsins and methods of using the mitoplatsins.

71 Claims, 11 Drawing Sheets